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Absorption, tissue distribution, metabolism, and elimination of decabrominated diphenyl ether (BDE-209) in rats after multi-dose oral exposure

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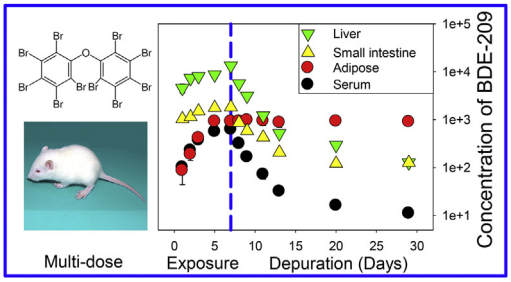
HIGHLIGHTS

- The tissue distribution patterns of BDE-209 are variable between the exposure and depuration periods.
- BDE-209 can be transferred from small intestine to liver through blood supply, and deposit in adipose.
- The half-lives of BDE-209 and its metabolites are dictated by the level of bromination and tissue functionality.

GRAPHICAL ABSTRACT



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ABSTRACT

Human and ecological risks of BDE-209 have drawn much attention, particularly with growing e-waste recycling activities in developing countries. To further address the issue of BDE-209 biotransformation, a laboratory-controlled study was conducted. Female Sprague-Dawley rats were dosed orally by gavage at a daily dose of 1 mg kg^{-1} body weight for 7 d and a depuration period of 22 d, to characterize absorption, distribution, metabolism, and elimination dynamics of BDE-209 during multi-dose exposures simulating short-term oral exposure of e-waste workers. The concentrations of BDE-209 in all tissues increased exponentially during the 7-d exposure period, indicating that multi-dose exposure could lead to increased accumulation of BDE-209 in rats. The liver accumulated the greatest amount of BDE-209 on a wet-weight basis, while adipose tissue had the highest concentration by the end of the 22-d depuration period. Half-lives of BDE-209, 207, and 197 during depuration were 1.1 ± 0.1, 2.7 ± 0.3, and 10.5 ± 3.1 d in serum and 0.9 ± 0.1, 2.2 ± 0.2, and 11.8 ± 2.3 d in liver, i.e., the half-life increased with decreasing level of bromination from deca- to octa-BDEs and was similar in both serum and liver. By contrast, the half-life of the debromination metabolite BDE-207 (21.7 ± 7.7 d) was longer in small intestine than in serum and liver, suggesting slower depletion of BDE-209 metabolites in small intestine. The metabolism of BDE-209 was not responsible for the occurrence of low brominated BDE congeners and OH– and MeO-PBDEs in human tissues.

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1. Introduction

Brominated flame retardants, especially polybrominated diphenyl ethers (PBDEs), have been widely used in electronic devices, furnishings, and building materials (Harrad and Abdallah, 2015; Meng et al., 2016; Xu et al., 2016). The manufacture and usage of commercial Penta-BDE and Octa-BDE are banned in Europe, Japan, and the United States (Jinhui et al., 2015). However, BDE-209, the major component of commercial Deca-BDE, continues to be produced in China, India, and Japan (Environment and Climate Change Canada, 2016) and is commonly found in the environment (Pan et al., 2016). BDE-209 has low acute toxicity (Costa and Giordano, 2011), but its debrominated, hydroxylated, and methoxylated metabolites have greater toxicity than the parent compound (Qiu et al., 2007; Huang et al., 2010; Wang et al., 2012b; Zhou et al., 2016). Low brominated BDE congeners (di- to hexa-BDEs), hydroxylated PBDEs (OH-PBDEs), and methoxylated PBDEs (MeO-PBDEs) have been frequently detected in human tissues (Lacorte and Ikonomou, 2009; Chen et al., 2013; Gao et al., 2015; Haraguchi et al., 2016). It is interesting to note that the concentrations of OH− and MeO-PBDEs (35 ± 29 and 7.7 ± 5.4 pg g^{-1} wet weight (ww)) in serum of residents from coastal areas were reported to be higher than those (16 ± 18 and 0.92 ± 1.8 pg g^{-1} ww) in workers of an e-waste recycling zone (Eguchi et al., 2012). The central issue is whether the degradation of BDE-209 and/or other sources are responsible for the occurrence of low brominated BDE congeners (di- to hexa-BDEs), as well as OH− and MeO-PBDEs in human tissues. Therefore, it is important to fully understand the mechanisms for absorption, distribution, metabolism, and elimination of BDE-209 in human.

Various animals of both mammalian and non-mammalian origins have been used as model organisms for laboratory studies. Mammals are particularly suitable for examining the safety of new drugs and for studying toxicokinetics. Mammalian animal models, such as rats, have been widely used to simulate the toxicokinetics of BDE-209 in humans. There are two oral exposure models for rats, i.e., single dose and multi-dose exposure. Morck et al. (2003) found that 90% of BDE-209 was excreted via feces after a single oral dose of ^{14}C-labeled BDE-209 in rats, resulting in 10% of the BDE-209 dose accumulated in the animals based on mass balance. For humans, the exposure of computer technicians (Jakobsson et al., 2002), workers dismantling electronics (Muenhor et al., 2010) and manufacturing or handling flame-retarded rubber (Thuresson et al., 2005), and the general pollution to BDE-209 is expected to be a continuous process. In this regard, a multi-dose exposure would more closely mimics the scenarios of actual occupational and non-occupational exposure. Recent studies mostly focused on the tissue distribution and transformation of BDE-209 in dosed rats at the end of multi-dose exposures (Huwe and Smith, 2007; Zhang et al., 2011; Yang et al., 2014). Because accumulation of abundant BDE-209 often occurs under multi-dose exposure conditions (Cai et al., 2011), the accumulation and depuration kinetics of BDE-209 and its metabolites under a multi-dose exposure scenario should be considered for better risk assessment of BDE-209. At the same time, it is also important to clarify any possible alterations in the distribution and absorption of BDE-209 during the entire exposure period.

To fill the above-mentioned knowledge gap, Sprague-Dawley rats were continually exposed to BDE-209 for 7 d and then allowed to depurate for 22 d, to elucidate the temporal distribution patterns of BDE-209 and its metabolites. The objectives of the present study were to (1) characterize the tissue distributions of BDE-209 in dosed rats during the uptake and depuration periods; (2) identify the metabolites of BDE-209 in dosed rats; and (3) estimate the half-lives of BDE-209 and its metabolites in different tissues of rats after a multi-dose exposure.

2. Materials and methods

2.1. Materials

Eight individual BDE congeners, including BDE-28, 47, 99, 100, 153, 154, 183, and −209, surrogate standards (BDE-51, BDE-115, and 4′-fluoro-2,2′,3,3′,4,5,5′,6,6′-nonabromodiphenyl ether (F-BDE-208)) and internal standards (BDE-69, 3-fluoro-2,2′,4,4′,5,6-hexabromodiphenyl ether (F-BDE-139), and 4′,6-difluoro-2,2′,3,3′,4,5,5′,6′-octabromodiphenyl ether (F-BDE-201)) were purchased from AccuStandard (New Haven, CT, USA). Standard solutions of individual OH-PBDEs (4′-OH-BDE-17, 2′-OH-BDE-28, 3-OH-BDE-47, 5-OH-BDE-47, 6-OH-BDE-47, 4′-OH-BDE-49, and 2′-OH-BDE-68) were also purchased from AccuStandard (New Haven, CT, USA). Standard mixtures of BDE congeners (BDE-194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, and 209), MeO-PBDEs (5-MeO-BDE-47, 6-MeO-BDE-47, 4′-MeO-BDE-49, 2′-MeO-BDE-68, 5′-MeO-BDE-99, 5′-MeO-BDE-100, 4′-MeO-BDE-101, and 4′-MeO-BDE-103), and ^{13}C-OH-PCB-61 were purchased from Wellington Laboratories (Guelph, Canada). BDE-209 from Tokyo Chemical Industry (Tokyo, Japan) was used for the exposure experiment. Anhydrous sodium sulfate was dried at 450 °C for 6 h and silica gel was activated at 110 °C for 4 h. Acid silica gel was prepared by mixing activated silica gel with concentrated sulfuric acid (H_2SO_4) at a weight ratio of 1:1.

2.2. Animal exposure experiments

Female Sprague-Dawley rats (200 ± 20 g) were purchased from the Guangzhou University of Chinese Medicine. The animal protocols used in the present study were in compliance with laboratory animal regulations of the Institute of Laboratory Animal Science, Jinan University. All rats were raised under standard housing conditions (12 h light/dark cycle and 20 ± 2 °C) and were acclimated for one week beforehand. Rats were randomly divided into dosed and control groups. Three rats were housed in a cage with water supplied ad libitum but fed separately. The spiked corn oil was prepared by dissolving 50 mg of BDE-209 in corn oil (500 mL), which was stirred by a magnetic stirrer until BDE-209 was completely dissolved. The actual concentration of BDE 209 was 0.13 ± 0.02 mg mL^{-1} in the final solution. The gavage volume was 1 mL of oil per 100 g body weight for each rat per day. As a result, individual rats were administered with BDE-209 by oral gavage at a dose of 1 mg of BDE-209 per kg of rat body weight per day during a 7-day exposure period, followed by depuration for 22 days. Control groups were also exposed to corn oil at the same dose volume. Rats were sacrificed 24 h after gavage by anesthetizing and exsanguinating with venipuncture. Dosed rats were sacrificed on day 0, 1, 2, 3, 5, 7, 8, 9, 11, 13, 20, and 29, whereas control rats were also sacrificed on day 0, 7, and 29. Each rat was dissected to collect blood, liver, small intestine, and adipose (abdominal adipose). Upon collection, small intestine samples were rinsed with water and blood samples were allowed to coagulate before serum was prepared through centrifugation (Sigma 3K15, Darmstadt, Germany) for 20 min at 3000×*g* (Grimm et al., 2015). All samples were frozen at −20 °C immediately until extraction.

2.3. Sample extraction

Liver, small intestine, and adipose samples were homogenized, freeze-dried, and ground into fine powders. An aliquot of each sample (0.2–2 g) was spiked with the surrogate standards (BDE-51, BDE-115, and F-BDE-208) and sonicated three times, each with

40 mL of a 2:2:1 mixture by volume of hexane, dichloromethane, and acetone. The extracts were combined and concentrated, solvent-exchanged to hexane, and condensed to approximately 20 mL with a Zymark TurboVap 500 (Hopkinton, MA, USA). Ten milliliters of concentrated H_2SO_4 were added to the extract to remove lipids. The mixture was shaken for 5 min and separated by centrifugation at 4000×*g* for 5 min, after which the upper hexane layer was collected. The H_2SO_4 layer was washed three times, each with 10 mL of hexane. The combined hexane extract was concentrated to approximately 1 mL, then purified with a glass column packed with 1 cm of anhydrous sodium sulfate, 10 cm of acid silica gel, 3 cm of neutral silica gel, and 1 cm of anhydrous sodium sulfate from bottom to top. The fraction containing PBDEs was eluted with 30 mL of dichloromethane. The effluent was concentrated, solvent-exchanged to hexane, further concentrated to 0.2 mL, and spiked with the internal standards before instrumental analysis. The subsamples were analyzed for MeO-PBDEs and OH-PBDEs using a protocol adapted from Sun et al. (2012), detailed in the Supplementary Data.

2.4. Quality assurance and quality control

A preliminary testing demonstrated that no PBDEs were detected in the corn oil used to prepare rat feed. Two procedural blanks, three spiked blanks, and three spiked samples were analyzed for each batch of 20 samples. Respective recoveries of surrogate standards BDE-51, BDE-115, and F-BDE-208, were 86 ± 10%, 82 ± 10%, and 69 ± 11% in serum samples, and 97 ± 18%, 97 ± 19%, and 90 ± 18% in other samples. Concentrations were not corrected for surrogate recoveries. In addition, a standard solution of BDE-209 was injected after every 10 samples was repeatedly analyzed, to ensure that any thermal degradation of BDE-209 during analysis was lower than 5%. The lowest calibration concentration of a target analyte multiplied by the final extract volume and divided by the actual sample mass was defined as the reporting limit. In the present study, the reporting limit for BDE-209 was 1.0 ng g^{-1} ww for the liver, small intestine, and adipose samples and 3.3 ng g^{-1} for serum sample, whereas those for other BDE congeners were 0.1 ng g^{-1} ww and 0.33 ng g^{-1}, respectively.

2.5. Data analysis

The accumulation kinetics of an individual BDE congener in dosed rats was described by a first-order rate, one-compartment model (Leppanen and Kukkonen, 2004):

$$C_t = a\left(1 - e^{-bt}\right) \quad (1)$$

where C_t is the concentration of a BDE congener in a rat tissue at a given time (t) in the exposure period; a and b are fitting parameters. The depuration kinetics of a target analyte in dosed rats was fitted to a first-order elimination model (Oberg et al., 2002):

$$C_t^{'} = C_0 \times e^{-k_e t} \quad (2)$$

where $C_t^{'}$ is the concentration of a BDE congener in a rat tissue at a given time (t) in the depuration period; C_0 is the concentration of PBDEs at the beginning of the depuration process; t is the depuration time in the range of 0–22 d; and k_e is the elimination rate (d^{-1}). The half-life ($t_{1/2}$) of a target analyte in a given rat tissue was calculated by

$$t_{1/2} = \frac{\ln 2}{k_e} \quad (3)$$

The statistical software SPSS 17.0 (Chicago, IL, USA) was used to analyze the data. Concentration data were compared using a paired *t*-test. Significance was set at $p < 0.05$.

3. Results and discussion

3.1. Evaluation of rats' health and growth

The daily dose used (1 mg BDE-209 per kg of body weight) in the present study was 2–3 orders of magnitude lower than those used in previous studies (Norris et al., 1975; Yang et al., 2014). Therefore, the growth of the dosed rats were not significantly impacted by the administration of BDE-209, as body weights were not significantly different between the dosed and control groups during the exposure period (Fig. S1). In addition, no visible behavioral toxicity for dosed rats was observed during the exposure period. Before gavage, the concentrations of BDE-209 in rat tissues were below the reporting limit in both the control and dosed groups. The BDE-209 concentrations in tissues of control animals were also below the reporting limit throughout the experiment.

3.2. Tissue-specific distribution of BDE-209 in dosed rats

The tissue distribution patterns of BDE-209 on a wet weight basis were different between the exposure and depuration periods (Fig. 1). Specifically, it was stable over the exposure period, with 75–82% and 1.5–8.0% of BDE-209 accumulated in liver and adipose, respectively. This was consistent with the findings from most previous studies on oral dosing of BDE-209 in rats, i.e., higher concentrations occurred in liver than in other tissues upon exposure (Morck et al., 2003; Huwe and Smith, 2007; Huwe et al., 2008). In contrast, the relative abundance of BDE-209 decreased from 79% to 11% in liver, but increased from 12% to 77% in adipose tissue during depuration (Fig. 1). On an absolute scale, the BDE-209 concentration in adipose changed from 915 ± 143 to 895 ± 88 ng g^{-1} ww over the depuration period, but was not statistically significant ($p = 0.85$). By comparison, the BDE-209 concentration in liver decreased significantly ($p < 0.01$) from 13,000 ± 1000 to 127 ± 7.5 ng g^{-1} ww, i.e., BDE-209 was eliminated faster from liver than from adipose. The tissue distribution patterns of BDE-209 based on lipid weight were also different in dosed rats between the exposure and depuration periods. The large variability in relative and absolute tissue concentrations of BDE-209 observed in the present study suggests that any snap-shot field measurements of biota are not necessarily representative of the extent of contamination in them (Sonne et al., 2015).

The liver had the highest lipid-normalized concentration (360 ± 28 μg g^{-1}) of BDE-209, followed by serum (270 ± 11 μg g^{-1}), small intestine (120 ± 5.2 μg g^{-1}), and adipose (1.5 ± 0.23 μg g^{-1}) at the end of the 7-d exposure. This seems to indicate that lipophilicity is not the only crucial factor to tissue distribution of BDE-209 in dosed rats. Another interpretation is that the blood supply rate dominates the tissue distribution of BDE-209, i.e., the majority of BDE-209 is concentrated rapidly in the tissues highly perfused by blood, such as the liver. A previous study also found that plasma and blood-rich tissues contained the highest lipid-normalized concentrations of BDE-209 while adipose contained the lowest concentration in rats exposed to a single oral dose of ^{14}C-labeled BDE-209 (Morck et al., 2003). Apparently, the strong binding affinity of BDE-209 to plasma proteins may facilitate its transport in the blood-rich tissues (Charman, 2000). On the other hand, the tissue distribution of BDE-209 was different from that of BDE-47, which was mainly accumulated in adipose and skin of rats subject to a single oral dose of this congener (Staskal et al., 2005). The bioconcentration factor of BDE-47 was 0.19 and 11.71 in liver and

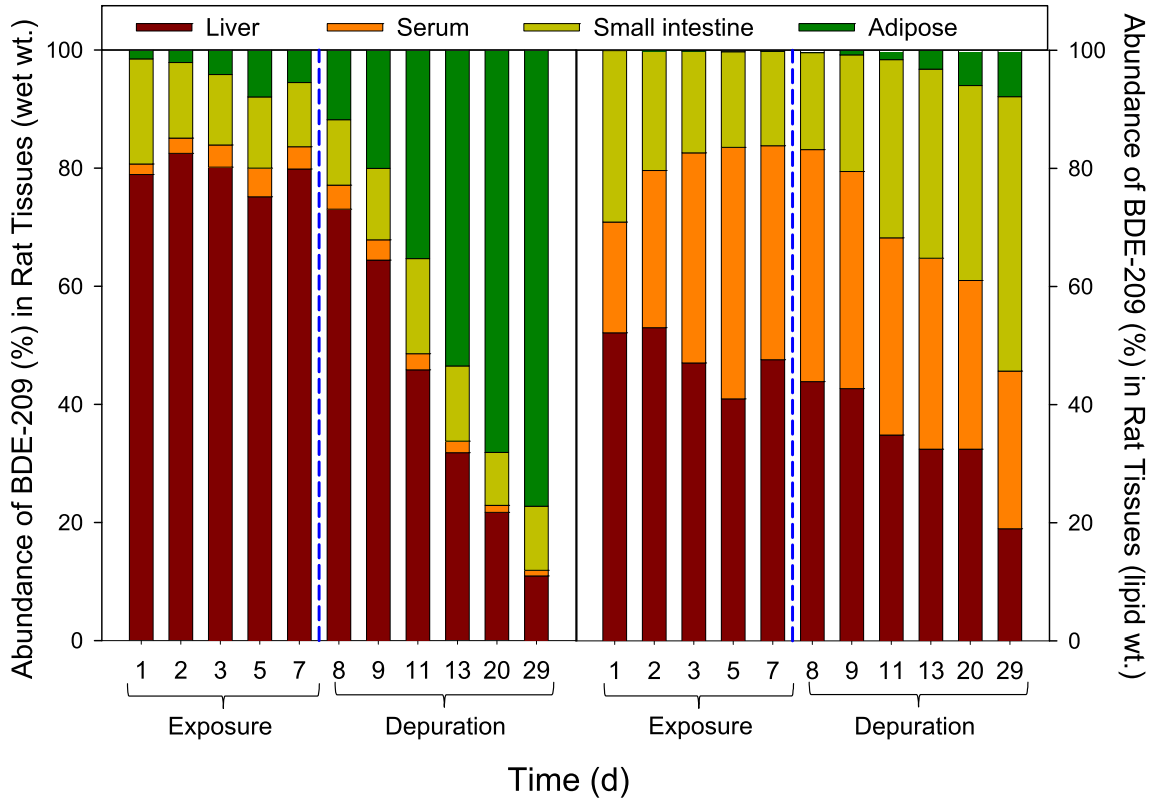

Fig. 1. Relative contributions of BDE-209 in individual tissues (liver, serum, small intestine, and adipose) to its total concentrations in rats based on wet weight and lipid weight. Rats were exposed to BDE-209 through diet for 7 d and depleted for 22 d.

adipose of rats exposed to PBDEs (BDE-28/33, 47, 85, 99, 100, 138, 153, 154, 183, 196, 197, 203, 206, 207, and 209) in the ground rat chow topped with spiked corn oil, while that of BDE-209 was 0.38 and 0.14, respectively (Huwe et al., 2008). Although log K_{ow} of BDE-209 (9.87) is greater than that of BDE-47 (6.80) (Bao et al., 2011), BDE-209 was not as accumulated in adipose tissue as much as BDE-47. The difference in bioconcentration factors was attributed to different molecular weights of BDE-47 (485.8) and BDE-209 (959.2) (Narvaez Valderrama et al., 2016). It may be more difficult for BDE-209 to traverse the cell membrane and accumulate in the adipose than BDE-47, suggesting stronger molecular interaction between cell membranes and BDE-209 (Bao et al., 2011). Overall, the tissue distribution of BDE-209 in dosed rats was largely dictated by the blood supply rate, tissue lipid content, and molecular weight.

3.3. Tissue-specific uptake and depuration of BDE-209

BDE-209 was detected in all rat tissues in the dosed group after 1-d exposure, revealing fast uptake and assimilation kinetics. The concentrations of BDE-209 in all tissues increased exponentially and did not reach steady-state during the 7-day exposure period (Fig. 2), which confirms that the multi-dose exposure could lead to increased accumulation of BDE-209 in rats (Cai et al., 2011). The absorption efficiency of BDE-209 in various tissues was calculated by multiplying concentration of BDE-209 in specific tissue with the corresponding weights of these samples, which was divided by the amount of BDE-209 in the dosed corn oil. The absorption efficiency of BDE-209 in rats tissues followed the sequence of liver (changed from 18 to 8.0%) > small intestine (5.0–0.94%) > adipose (0.35–0.66%) during the 7-day exposure period. The absorption efficiency was consistent with the percentage of an administered dose absorbed across the gastrointestinal tract ranged from approximately 7–26% based on the oral dosing rats studies (Morck et al., 2003; Sandholm et al., 2003).

During the depuration period, the BDE-209 concentrations in serum, small intestine, and liver decreased by 89%, 76%, and 91%, respectively, within the first four days and then leveled off afterwards (Fig. 2). The elimination curves of BDE-209 in serum, small intestine, and liver were well fitted by first-order depuration kinetics, with R^2 ranging from 0.94 to 0.99 and p values less than 0.0003. Elimination rates for BDE-209 were estimated at 0.64, 0.50, and 0.75 d^{-1} in serum, small intestine, and liver, respectively. On the other hand, no BDE-209 depuration was observed in the adipose of rats, i.e., elimination of BDE-209 from adipose was slow. This was expected as adipose is the storage tissue for hydrophobic chemicals in rat. The concentrations of BDE-209 in small intestine and serum were strongly and positively correlated ($r^2 = 0.83$ and $p < 0.0001$; Fig. 3a). The serum and liver concentrations of BDE-209 in dosed rats were also significantly correlated ($r^2 = 0.89$ and $p < 0.0001$; Fig. 3b). These results suggested that BDE-209 could be transferred from small intestine to liver through blood supply, and finally deposit in adipose.

3.4. In vivo degradation of BDE-209

Because BDE-209 can be photodegraded in the environment, precaution was taken to minimize the exposure of all samples to light. Direct light irradiation to the samples was minimized during the cleanup and storage processes in the laboratory. To examine whether BDE-209 was debrominated during the sample treatment processes, adipose samples from the control groups were spiked with BDE-209 and processed with the same procedures as the exposed samples. Hepta- to nona-BDEs only accounted for 1.9% and 3.8% of total BDE (sum of BDE-183, 196, 197, 201, 206, 207, 208, and

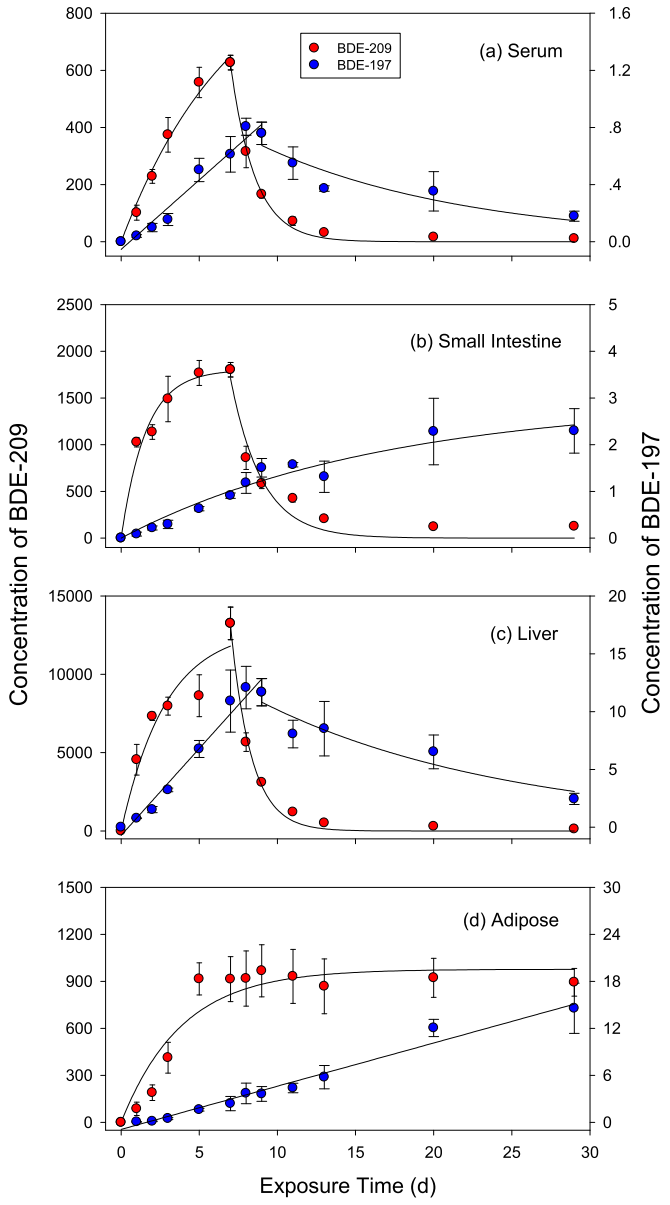

Fig. 2. Accumulation and depletion kinetics of BDE-209 and BDE-197 in the serum (a), small intestine (b), liver (c), and adipose (d) of rats. Rats were exposed to BDE-209 through diet for 7 d and depleted for 22 d. The concentrations of BDE-209 and BDE-197 in different tissues were expressed in ng g^{-1} wet weight.

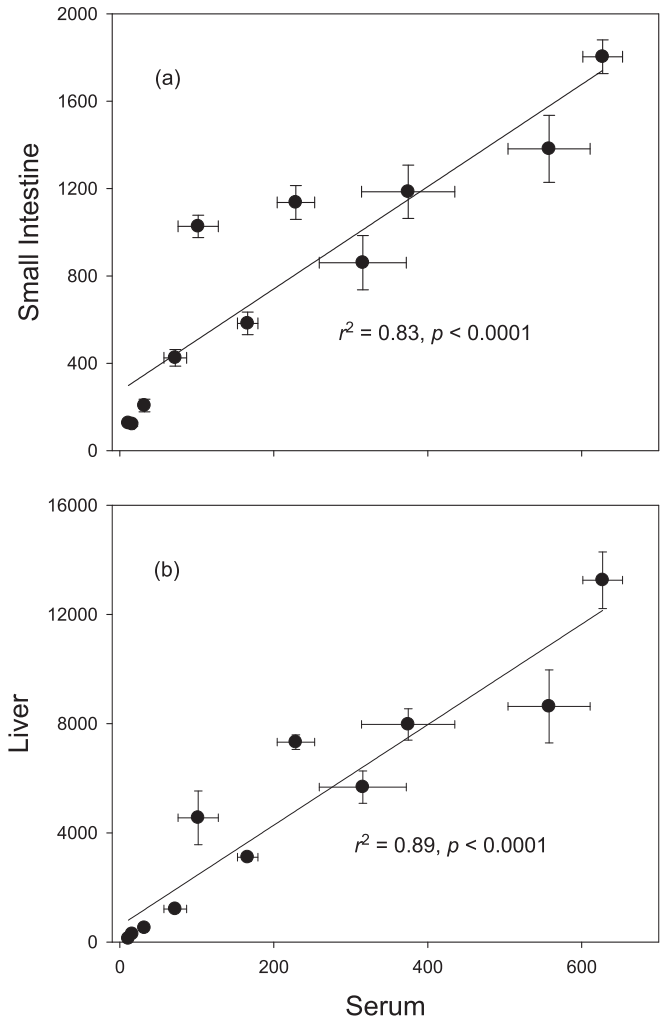

Fig. 3. Correlations of BDE-209 concentrations (ng g^{-1} wet weight) between small intestine and serum (a) and serum and liver (b) at exposure time of 29 d.

209) concentrations in the dosed corn oil and spiked control adipose samples, respectively, indicating insignificant debromination of BDE-209. By comparison, hepta- to nona-substituted BDE congeners in the dosed rat tissues comprised 9–29% of total PBDEs at the end of the depuration experiment, and their concentrations increased with exposure time (Fig. S3). Although trace amounts of lower-brominated BDEs in rat tissues may have been derived from the dosed corn oil, the majority of these BDE congeners should have resulted from the debromination of BDE 209. Previous studies also demonstrated that BDE-209 could be metabolized to lower-brominated BDEs in rats (Huwe and Smith, 2007; Cai et al., 2011; Zhang et al., 2011).

The main metabolites of BDE-209 were similar in different tissues. BDE-196, 197, 201, 206, 207, and 208 were detected in liver and adipose of exposed rats, whereas BDE-197 and BDE-207 were the major congeners of octa-BDE and nona-BDE homologue groups, respectively (Fig. S3). Two previous studies also obtained similar results with rats dosed with BDE-209 (Huwe and Smith, 2007; Zhang et al., 2011). Debromination products of BDE-209 in serum and small intestine include BDE-197, 206, 207, and 208. BDE-196 and BDE-201 were not detected in these samples, ascribed to the small sample volumes of serum (2.7 ± 0.75 g ww) and small intestine (8.1 ± 1.6 g ww). MeO-PBDEs and OH-PBDEs were not detected in any tissues of the dosed rats, probably due to the low dose of BDE-209 (1 mg kg^{-1} body weight) and short exposure time (7 d) used in the present study. A previous study used a dose of 100 mg kg^{-1} body weight and exposure time of 20 d (Yang et al., 2014). The oxidation and methylation potential of BDE-209 appeared to be stronger in fish than rats, as MeO-BDE-47, MeO-BDE-68, MeO-BDE-100, OH-BDE-28, and OH-BDE-42 were observed in fish dosed by intraperitoneal injection for 22-d exposure to BDE-209 at 1 mg kg^{-1} body weight (Feng et al., 2015).

To identify the fate of metabolites from debromination of BDE-209 in the tissues of exposed rats, the accumulation and depuration kinetics of the main primary and secondary metabolites, BDE-207 and BDE-197, in serum, small intestine, liver, and adipose were examined. Similar to BDE-209, the concentrations of BDE-207 and BDE-197 in serum and liver continuously increased during the exposure period and decreased during depuration (Fig. 2a and c and Fig. S6a and S6c). Concentrations of BDE-197 in liver and serum

were significantly correlated with each other during the entire exposure experiment ($r^2 = 0.93$ and $p < 0.0001$; Fig. 4). On the other hand, an increasing trend was observed for BDE-197 in the small intestine and adipose in the depuration period (Fig. 2b and d), which was different from BDE-209 and BDE-207 (Fig. S6b and S6d). Morck et al. (2003) observed a larger fraction of covalently bound radioactivities in small intestine wall (61%) than in liver (29%) of rats exposed to a single oral dose of ^{14}C-labeled BDE-209 during depuration, i.e., small intestine possessed slower elimination rates of BDE-209 and its metabolites than liver. Although BDE-209 may have been debrominated in small intestine, considerably higher concentrations of BDE-197 in liver than in small intestine suggested that debromination mainly occurred in liver. It was likely that the low elimination rates of BDE-197 from small intestine and adipose were responsible for its continuously rising concentrations in these issues during depuration (Fig. 2b and c).

3.5. Estimated half-lives of selected BDE congeners

Because BDE-197 concentrations continuously increased in small intestine and adipose during depuration (Fig. 2b and c), their elimination half lives in these tissues could not be estimated. The half-lives of BDE-209 in the serum, liver, and small intestine of exposed rats were estimated at 1.1 ± 0.1, 0.9 ± 0.1, and 1.4 ± 0.3 d, respectively (Table 1). These values were close to the half-lives of 1.2 and 0.7 d in plasma and liver of rats upon dietary exposure to commercial BDE-209 (Huwe and Smith, 2007). A previous study also showed that BDE-209 was depleted rapidly with a terminal half-life of 2.5 d in rat plasma (Sandholm et al., 2003). The half-life of BDE-209 was estimated at 13–17 d for kestrels (Letcher et al., 2014), 50 ± 17 d for juvenile carp, and 43 ± 8 d for juvenile common sole (Munschy et al., 2011). It seems that BDE-209 eliminates more rapidly in mammals than in vertebrates, such as bird and fish. On the other hand, BDE-209 remained at an elevated level in adipose after 22 days of depuration (Fig. 2d), which was also observed in the blubber of dosed seal after 29 days of depuration (Thomas et al., 2005). Apparently BDE-209 can be eliminated in rat serum, liver, and small intestine, but accumulated in adipose for a long period of time, e.g., one month. It is therefore important to clarify the role of adipose in eliminating lipophilic organic compounds such as PBDEs and organochlorine pesticides from mammals.

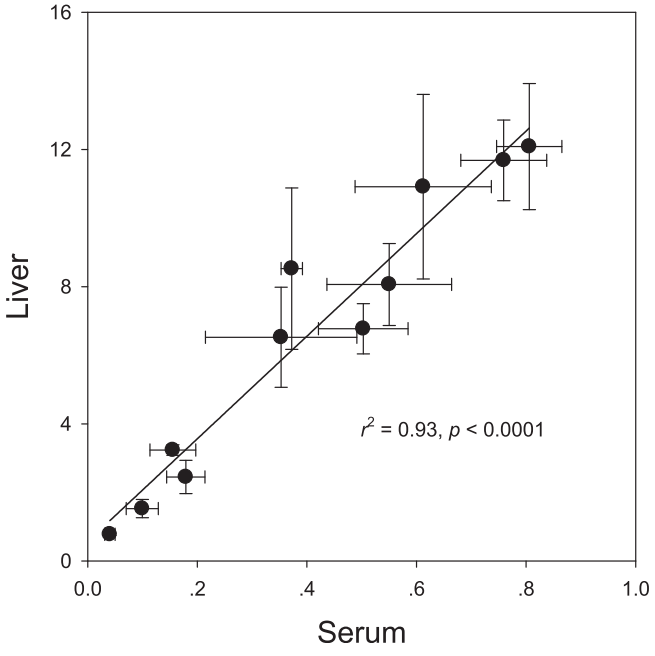

Fig. 4. Correlation of BDE-197 concentrations (ng g^{-1} wet weight) between serum and liver at day 29 of exposure.

Table 1
Half-lives calculated for select PBDEs in rats dosed with BDE-209 for 7 days followed by 22 days of depuration.

Tissue	Compounds	Half-live	R^2
Serum	BDE-209	1.1 ± 0.1	0.99
	BDE-208	4.7 ± 1.2	0.87
	BDE-207	2.7 ± 0.3	0.98
	BDE-206	8.8 ± 2.6	0.80
	BDE-197	10.5 ± 3.1	0.81
Liver	BDE-209	0.9 ± 0.1	0.99
	BDE-208	4.9 ± 2.3	0.62
	BDE-207	2.2 ± 0.2	0.98
	BDE-201	12.0 ± 5.2	0.70
	BDE-197	11.8 ± 2.3	0.91
Small intestine	BDE-209	1.4 ± 0.3	0.94
	BDE-207	21.7 ± 7.7	0.66

Half-life were yielded by ln 2 dividing the desorption rates, which were derived by fitting kinetic data with a one-order depuration model (Equation (2)). Correlation coefficient (R^2) was the fitting magnitude index of kinetic data.

The half-lives of BDE congeners in serum and liver increased with decreasing bromination from deca- to octa-BDEs. For example, the half-lives of BDE-209, 207, and 197 in serum and liver were 1.1 ± 0.1, 2.7 ± 0.3, and 10.5 ± 3.1 and 0.9 ± 0.1, 2.2 ± 0.2, and 11.8 ± 2.3 d, respectively. This was consistent with Huwe et al.'s finding that the half-lives of BDE-209, 207, and 197 were 1.2, 7.9, and not available in serum and 0.7, 4.7, and 6.9 d in liver of rats exposed to BDE-209 (Huwe and Smith, 2007). The half-life of BDE-207 was longer in small intestine than in liver, further confirming that depletion of BDE-209 metabolites was slower in small intestine than in liver. A previous study obtained similar half-lives of BDE-207 as 7.9, 4.7, and 22.6 d in serum, liver, and carcass of rats, respectively (Huwe and Smith, 2007). As the half-lives of BDE congeners were variable in different tissues, the half-lives in serum may not be reflective of the elimination rates of persistent organic pollutants, such as PBDEs and polychlorinated biphenyls, in rats.

Although the half-lives of BDE-209 and its metabolites are short, higher-order metabolites, such as BDE-47 and MeO- and OH-PBDEs, were not detected in any dosed rat tissues. It is interesting to note that abundant MeO- and OH-PBDEs were found in serums of e-waste dismantling workers (Ren et al., 2011) and residents from coastal and rural areas, such as Japan (Haraguchi et al., 2016), Chidambaram of India (Eguchi et al., 2012), Hong Kong (Wang et al., 2012a), and Duong Quang of Vietnam (Eguchi et al., 2015). The daily dietary dose of BDE-209 used in the present study (200 μg) was much higher than the daily dietary uptakes of PBDEs by residents in non-e-waste recycling zones (Canada: 44 ng (Jones-Otazo et al., 2005); Span: 82–97 ng (Bocio et al., 2003); France: 33 ng (Rivière et al., 2014); China: 48 ng (Zhang et al., 2013); the United States: 5476 ng (Schecter et al., 2006); and Sweden: 51 ng (Darnerud et al., 2001)) and in e-waste recycling zones (2700–56000 ng) (Chan et al., 2013) assuming an average body weight of 60 kg. The discrepancy in the amounts of parent BDE congeners and their MeO- or OH-PBDEs metabolites between human body and dosed rats suggested that contaminated foods, especially seafood, could be the major contributor to MeO- and OH-PBDEs in human serum. Fujii et al. (2014) also suggested that edible fish (*Serranidae* sp.) and seaweeds (*Sargassum fusiforme*) may be the sources of MeO- and OH-PBDEs in Japanese woman serum, where similar profiles of MeO- and OH-PBDEs were observed.

4. Conclusions

The tissue-specific distribution of BDE-209 in dosed rats is largely dictated by the blood supply rate, tissue lipid content, and molecular weight. BDE-209 can migrate from small intestine to liver through blood supply, and finally deposit in adipose. The half-lives of BDE-209 and its debromination metabolites, derived from elimination kinetics, are related to the degree of bromination and the functionality of the tissues. Because the metabolism of BDE-209 is not responsible for the occurrence of low brominated BDE congeners (di- to hexa-BDEs), as well as OH− and MeO-PBDEs, in human tissues, risk assessments of these metabolites should be conducted based on other sources.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.chemosphere.2017.08.049.

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